Peace Corps
Technical Guideline 850

SCHISTOSOMIASIS

1. PURPOSE

- To provide Peace Corps Medical Officers (PCMOs) with guidance on schistosomiasis prevention, diagnosis and treatment.
- To provide PCMOs with guidance on in-service and close of service (COS) schistosomiasis testing of Volunteers.

2. BACKGROUND

Schistosomiasis, also known as "bilharzia", is a parasitic disease endemic to many areas of the world served by Peace Corps Volunteers. Among human parasitic diseases, schistosomiasis ranks second behind malaria in terms of socioeconomic and public health importance in tropical and subtropical areas. The disease is endemic in 74 developing countries and infects more than 200 million people. It is a serious disease that, if left undiagnosed and untreated, can result in major morbidity or mortality.

As such, the Office of Medical Services (OMS) attempts to: (1) prevent schistosomiasis infection in Volunteers, and (2) identify and treat those Volunteers who become infected during service. Components of this prevention and management strategy include:

- *Education:* the provision of education to PCMOs and Volunteers on schistosomiasis prevention measures, to include personal behaviors and strategies for avoiding exposure and interventions to reduce the risk of infection when exposure occurs.
- *Policy:* OMS policy that requires all Volunteers serving in schistosomiasis endemic areas to adhere to schistosomiasis infection prevention measures, i.e., avoidance of known risk areas and employment of risk reduction strategies throughout their Volunteer service.
- *Evaluation and Treatment:* evaluation and treatment, if medically indicated, of Volunteers with signs or symptoms consistent with schistosomiasis infection.
- *COS Screening:* screening for schistosomiasis via antibody testing at COS of all Africa Volunteers, all Volunteers leaving other schistosomiasis endemic areas, and all Volunteers who have traveled to schistosomiasis endemic areas during service.

  All COS antibody testing is conducted through the Centers for Disease Control and Prevention (CDC) using an enzyme-linked immunosorbent assay (ELISA) and immunoblot test. Volunteers with evidence of infection receive further evaluation and definitive medical treatment if clinically indicated.

The OMS Epidemiology and Surveillance Unit coordinates Peace Corps schistosomiasis case surveillance in collaboration with the CDC. In 2003 there were 38 clinical cases of schistosomiasis reported to the Peace Corps Epidemiology and Surveillance Unit. All 38 cases were reported from nine countries in the Africa region. Peace Corps also tests, via antibody testing, Volunteers without clinical symptoms in endemic countries. Such testing is conducted in-service when there is a significant exposure history, when microscopic examination of stool and urine for eggs is negative or not available, and at COS; in FY2003 there were 192 positive antibody tests for schistosomiasis, i.e., tests which indicated exposure and required treatment. In addition, due to the mild chronic form of the disease, schistosomiasis can also present in the Returned Peace Corps Volunteer population. When this occurs, cases are reported to the OMS Post-Service Unit. In 2003, 61 Volunteers filed post-service claims with the U.S. Department of Labor. These Volunteers completed service between 2000 and 2003.

3. GENERAL CONSIDERATIONS

Schistosomiasis occurs when human skin comes in contact with contaminated *fresh* water in which specific species of snails that carry schistosomes are living. Disease transmission occurs only in *fresh* water and only in areas where the specific *snail host* is present. Medical Officers and Volunteers should, however, assume that all rivers, streams, lakes, and other bodies of fresh water in schistosomiasis endemic areas are contaminated.

The pathophysiology of schistosomal disease reflects the geographic distribution and the unique life cycle of the parasite. Schistosomal disease results directly from schistosome eggs being deposited in host tissue and from the granulomatous host response to them. It is the eggs, not the worms, that are responsible for most of the pathology associated with the disease.

3.1 Geographic Distribution and Resistance Patterns

The three major species that infect humans are *S. haematobium* endemic in Africa and the Middle East, *S. mansoni* endemic in Africa, parts of South America, the Caribbean and the Middle East; and *S. japonicum* endemic in China, Southeast Asia, and the Philippines. Other species include *S. mekongi* located in the Mekong River area of Southeast Asia, and *S. intercalatum* located in Central and West Africa (see table below). **ATTACHMENT A** also provides a general illustration of the worldwide distribution of schistosomiasis.

Species	Geographic Distribution[1]
S. mansoni	**Africa -** southern Africa, sub-Saharan Africa, Lake Malawi, the Nile River valley in Egypt. **Middle East** - Iran, Iraq, Saudi Arabia, Syria, Yemen **South America** – including Brazil, Venezuela, Surinam **Caribbean –** Antigua, Dominican Republic, Guadeloupe, Martinique, Montserrat, St. Lucia (low risk).

[1] Centers for Disease Control and Prevention. *Fact Sheet Schistosomiasis.* Parasitic Disease Information. Division of Parasitic Diseases.

S. haematobium	**Africa -** southern Africa, sub-Saharan Africa, Lake Malawi, the Nile River valley in Egypt. **Middle East** - Iran, Iraq, Saudi Arabia, Syria, Yemen
S. intercalatum	**Africa** - southern Africa, sub-Saharan Africa, Lake Malawi, the Nile River valley in Egypt.
S. japonicum	**Asia -** Southern China**,** Indonesia, Philippines
S. mekongi	**Southeast Asia –** Philippines, Laos, Cambodia, Japan, central Indonesia, Mekong delta.

It is important to note that the prevalence of schistosomiasis is changing rapidly. Control programs have eliminated or nearly eliminated transmission of schistosomiasis in several countries. On the other hand, water resource development projects and population movements have led to introduction of schistosomiasis into regions and countries that were not endemic previously. Japan and Monteserrat have eliminated schistosomiasis, and at present there is believed to be minimal, or no risk, of schistosomiasis in Puerto Rico, Antigua, Guadelupe, Martinique, St. Lucia, Venezuela, Tunisia, Mauritius, Morocco, Iran, and Turkey.[2]

Resistance to praziquantel may be emerging after nearly 20 years of intensive use. Hycanthone resistance in *S. mansoni* is well documented. In regions of Egypt and Kenya where there has been heavy exposure to praziquantel, there are reports of *S. mansoni* and *S. haematobium* infections that are not responsive to multiple courses of treatment.

For additional information on schistosomiasis, PCMOs should refer the CDC's Division of Parasitic Disease website at www.dpd.cdc.gov/dpdx and to their book *Health Information for International Travel* – the "Yellow Book", also available at www.cdc.gov/travel/reference.htm.

3.2 Life Cycle of the Schistosome Parasite

The life cycle of the schistosome parasite requires the presence of human carriers, *fresh* water, and a species-specific intermediate snail host. Transmission occurs when the cercarial form of the parasite penetrates human skin. The basic life cycle is illustrated in **ATTACHMENT B** and is summarized below.

- Schistosoma eggs leave infected humans in feces and/or urine and hatch in fresh water releasing miracidia.
- The miracidia, in turn, infect specific species of freshwater snails where they transform into cercariae, i.e., the free-swimming larval form of the parasite.
- The snail releases the cercariae back into the water where they survive for about 48 hours and can penetrate human skin.
- After penetration, the cercariae shed their bifurcated tails, and the resulting schistosomula enter capillaries and lymphatic vessels enroute to the lungs.

[2] Centers for Disease Control and Prevention. *Health Information for International Travel, 2003-2004.*

- After several days, the worms migrate to the portal venous system, including the liver, where they mature and unite. Adult schistosomes are small worms, approximately 1-2 cm in length. They do not multiply within the human host and cannot be passed from person to person.
- Pairs of worms then migrate to species-dependent sites (see table in Section 5 below) in the venous system where eggs are produced and released. Egg production commences 4-6 weeks after infection for *S. japonicum*, 6-8 weeks after infection for *S. mansoni*, and 10-12 weeks after infection for *S. haematobium* and continues for the life of the worm – usually three to seven years. "Rarely, worms may live up to 30 years."[3]
- Eggs pass from the lumen of blood vessels into adjacent tissues, and pass through the intestinal or bladder mucosa and are shed in the feces (*S. mansoni* and *S. japonicu*m) or in urine (*S. haematobium*) - completing the cycle.

4. PREVENTION OF SCHISTOSOMISASIS INFECTION

At this time, no schistosomiasis vaccine is available, nor are any drugs approved as chemoprophylactic agents. As such, avoidance of exposure to contaminated water remains the only reliable prevention measure.

The Schistosoma parasites can penetrate the skin of persons who are wading, swimming, bathing, washing, or otherwise in contact with contaminated water. Therefore, to reduce or eliminate potential schistosomiasis exposure, OMS requires PCMOs to educate Volunteers on disease specific prevention measures. Education should include personal behaviors and strategies for avoiding exposure, country specific information that may assist Volunteers in avoiding exposure and disease specific interventions to reduce the risk of infection when exposure occurs.

The Office of Medical Services also requires all Volunteers serving in schistosomiasis endemic areas to observe schistosomiasis prevention measures. These include, but are not limited to, the following precautions.

- Avoid contact with all freshwater bodies of water; this includes *lakes, ponds, rivers, streams, irrigation systems, dams, canals and other bodies of freshwater.* All freshwater bodies of water in endemic areas are potentially contaminated.
- Do not swim in any of the freshwater sources mentioned above. Swim in well-maintained, chlorinated pools or in the sea. Neglected swimming pools are hazardous; they very quickly become inundated with snails.
- Do not bathe in any of the freshwater sources mentioned above. Bathe in safe water. Large quantities of water can be made safe by the following methods: (1) allowing the water to stand for *at least* 48 hours during which time the cercariae die; (2) heating the water for 5 minutes at 150º F; or (3) filtering and treating the water with iodine or chlorine in a manner similar to preparing drinking water.

[3] Martin S. Wolfe, MD, Infectious Disease, Director of Traveler's Medical Service of Washington, D.C..

- Be wary of swimming or bathing in oceans, beaches, lagoons, or bays near river or sewage outlets. These areas may also be contaminated.
- Never drink untreated water from any of the freshwater sources mentioned above. Drink safe water. Drinking water should be made safe using the water disinfection methods described in TG 810 Attachment A "Water Disinfection Methods".

Though several prevention measures associated water contact have been examined, e.g., application of DEET to the skin prior to freshwater exposure, vigorous towel drying after freshwater exposure, etc., none of these measures provide significant protection against schistosomal infection. The *only* measure that reliably prevents schistosomiasis is avoidance of contact with freshwater in endemic countries.

5. SCHISTOSOMIASIS EVALUATION & DIAGNOSIS

All Volunteers with signs or symptoms suggestive of possible schistosomiasis infection must be evaluated. The definitive diagnosis of schistosomiasis is made by identification of eggs in urine (*S. haematobium*), stool (all species), or a history of fresh water exposure in an endemic area *and* a positive antibody titer.

Species	Worm Location	Signs, Symptoms, End-Organ Disease
S. haematobium	Vesical plexus and veins draining the ureters and bladder	*Acute*: dysuria, haematuria, eggs in urine, CNS and pulmonary symptoms. *Chronic*: hydronephrosis, fibrosis, stricturing, calcification of urinary tract, bladder cancer
S. mansoni	Superior mesenteric veins around the intestines	*Acute*: diarrhea, fatigue, cramps, eggs in stool, CNS symptoms *Chronic*: portal hypertension, hepatic and intestinal fibrosis, rarely CNS symptoms
S. intercalatum	Superior mesenteric veins around the intestines	*Acute:* diarrhea, cramps, eggs in stool *Chronic:* portal hypertension
S. japonicum *S. makongi*	Inferior mesenteric and superior veins around the intestines hemorrhoidal veins	*Acute:* eggs in stool, jaundice, hepatomegaly, CNS symptoms *Chronic*: portal hypertension, hepatic and intestinal fibrosis, rarely CNS symptoms

5.1 Signs and Symptoms

Most Volunteers who become infected with schistosomiasis are asymptomatic, recall no symptoms of acute infection, and appear to have a light infection with few adult worms present. If symptoms are present, they vary according to the *stage* of infection and the *worm location* of the specific schistosome species (see table above).

The three clinical stages of schistosomal infection are:

Stage 1: Dermatitis	secondary to skin invasion by cercariae.
Stage 2: Acute	secondary to systemic hypersensitivity to egg and larval antigens.
Stage 3: Chronic	secondary to granulomatous reactions to eggs and egg antigens; if left untreated, results in fibro-occlusive disease.

Key symptoms and signs of *acute* and *early* chronic infection include the following:

KEY SYMPTOMS	KEY SIGNS
▪ History of freshwater exposure ▪ Fever ▪ Cough ▪ Malaise, Fatigue ▪ Arthralgias, Myalgias ▪ Abdominal pain ▪ Diarrhea (may be bloody) ▪ Urticaria	▪ Fever ▪ Right Upper Quadrant (RUQ) pain ▪ Hepatosplenomegaly ▪ Eosinophilia ▪ Hematuria, dysuria (chronic)

Schistosomal (Cercarial) Dermatitis

Schistosomal dermatitis is a pruritic, macular, or in some instances maculopapular, rash that occurs at the site of cercarial penetration. It is caused by schistosomes that have *human* hosts and is similar to, but less severe than, the *non-human* form of cercarial dermatitis known as "swimmers' itch" (see description below).

The reaction may develop a few hours after infection or may appear up to one week later, and may last a few hours to several days. At this early stage of infection, most people have no complaints and no clinical symptoms. Some may complain of burning or irritation of the skin followed, in some cases, by urticaria.

The differential diagnosis of schistosomal dermatitis includes allergy, insect bites, and contact dermatitis.

Swimmers' Itch

"Swimmer's itch" is an often misused term that refers to a form of cercarial dermatitis caused by schistosomes that have *non-human* hosts, e.g., birds, muskrats, beavers. While common in the U.S, especially in the Great Lakes region, this form of cercarial dermatitis it is rarely seen in the Peace Corps world. Non-human schistosome infection is limited to

the skin and does not progress to more serious forms of infection. Cercaria enter the skin where they die and produce an allergic reaction.

Acute Schistosomiasis ("Katayama Fever" or "Snail Fever")

The acute stage of infection, often known as "Katayama Fever" or "Snail Fever", typically occurs after heavy exposure to *S. japonicum* infection.[4] The syndrome may also be seen with *S. mansoni* and rarely with *S. haematobium*. The syndrome is most often seen in persons with no previous exposure to the disease; thus it is rarely seen among endemic populations. Acute symptoms are thought to be caused by a hyper-immune or serum sickness-like reaction to the schistosome eggs or immature worms being deposited into host tissue.

Symptoms usually develop 4-7 weeks after exposure to contaminated water, but may even develop months later. The onset of symptoms usually coincides with the onset of egg deposition and often precedes the appearance of eggs in urine or feces. Eggs, if found in urine or feces, typically appear 40-50 days after exposure but may take over 90 days to appear. By this time, the acute stage may be over, with symptoms having resolved over a period of several weeks.

Often the patient becomes suddenly ill with presentations varying from mildly ill with few symptoms to extremely ill with continuous symptoms. Symptoms include fever (99º-105º F), chills, nonproductive cough, headache, anorexia, weight loss, generalized myalgias, right-upper quadrant pain, and diarrhea (may be bloody). Respiratory symptoms have been reported in up to 70% of persons infected with *S. mansoni* but less frequently in those infected with *S. haematobium*. Tender hepatomegaly is usually present, and splenomegaly occurs in one third of cases.[5] Urticaria and or diarrhea occur in 25% of patients.[6] When the acute infection is massive in a patient with no previous exposure to schistosomes, the resulting illness can be serious and life threatening.

Early Chronic Schistosomiasis

Symptoms of *early chronic* disease may be seen in Peace Corps Volunteers. These symptoms usually appear 10-12 weeks after infection when some, of the many of thousands, of eggs released each day by an adult worm, reach the lumen of the bowel or bladder and cause inflammation of these organs. Symptoms of *intestinal* disease typically include fatigue, abdominal pain, vague, nonspecific intestinal complaints and diarrhea. The diarrhea may progress to dysenteric bloody diarrhea and subsequent iron deficiency anemia. Symptoms of *urinary tract* disease include dysuria and hematuria.

Early Neurologic Manifestations

[4] "Acute disease is more likely associated with *S. japonicum* than other species because the worms produce about 2000-3000 eggs per day, nearly 10 times the egg output of the female *S. mansoni*." (Rakel)
[5] Ross, A.G.P., Bartley, P. G., Sleigh, A. C. , et. al. Schistosomiasis, *New England Journal of Medicine*, Vol.. 346, No. 16, April 18, 2002, pg. 1214.
[6] Uniformed Services University of the Health Sciences, Schistosomiasis, *Tropical Medicine Central Resource*, Chapter 2.

Rarely, schistosomiasis involves the central nervous system (CNS). Egg deposition in the brain or around the spinal cord may produce seizures and/or a transverse myelitis-like syndrome. Cerebral mass lesions may result from egg deposition in or around brain tissue.[7] Most reported cases of cerebral schistosomiasis are caused by *S. japonicum*, and most cases of schistosomal tranverse myelitis, by *S. mansoni*. CNS disease caused by *S. haematobium* is rare. Symptoms of both syndromes may include severe headache and neck stiffness, central nervous system (CNS) changes, both generalized and focal, and paralysis. In severe cases infection may result in death.

Medical Officers should consider the possibility of neuroschistosomiasis in all patients who have a history of freshwater exposure in schistosomiasis endemic areas and CNS abnormalities, even in the absence of classic signs and symptoms of acute disease. Neuroschistosomiasis can occur several months after exposure to infested water and in low-intensity infections in which eggs may be undetectable or difficult to identify in urine or stool.[8]

Late Chronic Schistosomiasis

Late chronic disease is responsible for most of the morbidity and mortality associated with the disease. Chronic schistosomiasis occurs almost exclusively in lifetime residents of endemic areas and is very rarely seen in expatriates or Peace Corps Volunteers.

During *the late chronic* stage of infection, schistosome eggs, and the antigens they secrete, can accumulate in target organs, which eventually results in granuloma formation, scarring and fibrosis. The intensity and duration of infection determine the amount of antigen released and the severity of fibro-obstructive disease. *S. haematobium* affects the urinary tract, i.e., the bladder, ureters, and kidneys, and *S. mansoni, S. japonicum, S. mekongi*, and *S. intercalatum* affect the intestine and liver. Neuroschistosomiasis can also occur years after initial infection, though this is less common than in the early chronic phase

5.2 Physical Exam

Physical findings vary with the stage of the illness, worm location, worm burden, and target-organ involvement.

Schistosomal Dermatitis

- *Skin:* Nonspecific, erythematous, macular or maculopapular rash. Vesicles may be present. No particular patterns are observed, except that the rash is found only on areas of skin that came into contact with the infected water. No other symptoms are present

[7] Biopsies show granulomatous lesions with relatively few eggs. Spinal involvement may be due to a granulomatous mass or impairment of spinal blood supply.
[8] Cetron, M. S., CDC Recommendations for Health Care Providers Evaluating Persons Enrolled in the Schistosomiasis Study in Malawi: March-April, 1993

Acute and Early Chronic Schistosomiasis

- *Vital Signs:*
  - Temperature may range from normal to 105˚F (40.6˚C); blood pressure, respiratory rate and pulse may be elevated secondary to fever.
- *Skin:*
  - Nonspecific, erythematous, macular or maculopapular rash. Petechial rash or urticaria may be present.
- *Chest:*
  - Lungs: normal, cough
  - Cardiac: normal
- *Abdomen*:
  - Generalized tenderness to palpation may be present.
  - Spleen: moderate splenomegaly
  - Liver: RUQ tenderness with hepatomegaly
- *Extremities:*
  - Peripheral edema is usually absent.
  - Paralysis, if neurologic involvement.
- *Lymphadenopathy:*
  - May be generalized and present.
- *Musculoskeletal:*
  - Despite complaints of myalgia and arthralgia, neither muscle tenderness nor joint effusions are present.
- *Neurologic:*
  - Seizures and/or altered mental status if CNS involvement.
  - Paralysis

5.3 Laboratory Diagnosis and Findings

The detection of schistosome eggs in urine or feces is diagnostic of schistosomiasis. Because intensity of infection is associated with morbidity, quantitative assessment of eggs is important for determining severity of infection, but not necessary for diagnosis or treatment.

If there is no history of previous schistosomiasis infection, a positive serologic antibody titer in a Volunteer is also considered diagnostic of the disease. Medical Officers should initiate treatment if eggs are identified in urine or stool or if a positive serologic antibody titer is obtained.

KEY LABORATORY TESTS

- Urinalysis with microscopic examination; concentration and examination of 24 hour urine collection may be required to detect eggs.
- Stool specimen with microscopic examination; concentration and examination of 24 hour stool collection may be required to detect eggs.
- Complete blood count with peripheral smear
- Liver function tests (ALT, AST, direct/indirect billirubin, albumin)
- Antibody testing Enzyme-linked immunosorbent assay (ELISA) and species specific immunoblot

Urinalysis and Urine Microscopy

To detect eggs of *S. haematobium,* a urinalysis with microscopy must be performed whenever schistosomiasis is suspected.[9] Medical Officers should identify the best available in-country laboratory able to perform this exam.

S. haematobium egg excretion peaks between 10 a.m. and 2 p.m., thus samples should ideally be obtained around noon when excretion is maximal. Because eggs are not shed at a steady rate during the day, egg identification may be improved with concentration and examination of a 24-hour urine collection. Urinary protein excretion parallels egg excretion and also peaks at noon; erythrocyte excretion is delayed about 6 hours, and white blood cell excretion is bimodal at noon and 6 p.m.

All urine samples should be examined *qualitatively* after centrifuging as gross and microscopic hematuria is common. In moderate to heavy infections, eggs are almost always present on routine examination of urinary sediment. In lighter infections, routine urinalysis does not always reveal eggs and concentration techniques that improve egg identification should be used. Concentration techniques include: (1) centrifugation, (2) concentration of 24-hour urine collection, and (3) sedimentation or filtration (Nucleopore® membrane or nytrel filter) of a 10 ml volume of urine.

Quantitative egg counts are important for determining the severity of infection and the response to therapy, but are *not necessary* in order to provide treatment. The number of eggs per 10 ml of urine is the most commonly expressed estimate of intensity of current infection. Egg count findings may be interpreted as follows:

Number of Eggs *(per 10 ml of Urine or 1 gm of feces)*	**Severity of Infection**
< 100	Light
101 - 250	Moderate
> 250	Severe

[9] Very rarely are eggs found in the urine in infections with *S. japonicum.*

Stool Examination and Stool Microscopy

To detect eggs, a stool specimen examination with microscopy must be performed whenever schistosomiasis is suspected. Medical Officers should identify the best available in-country laboratory able to perform this exam. Eggs can be present in the stool in infections with *all* Schistosoma species, but are especially common in infections with *S. mansoni* and *S. japonicum.*

A stool specimen of 2-10 mg of fecal material with or without suspension in saline is required for examination. Stool specimens may be positive for heme or grossly bloody. Since eggs may be passed intermittently or in small amounts repeat examinations - as many as three specimens - may be required for diagnosis. Concentration and examination of a 24-hour stool collection or other concentration techniques that improve egg identification may be required. Concentration techniques are available and include: (1) the Ritchie technique; best for identification of light infections; (2) the Kato-Katz thick smear technique; requires 20-50 mg of fecal material and is frequently used to quantify egg burden; and (3) formalin-based examination techniques.

Quantitative egg counts are important for determining the severity of infection and the response to therapy, but are *not necessary* in order to provide treatment. The number of eggs per 1gram of stool is the most commonly expressed estimate of intensity of current infection. See above table for interpretation of egg count findings.

Serology (Antibody Detection)

Medical Officers should review Section 6 “Treatment of Schistosomiasis” and **ATTACHMENT D** for guidance on managing sero-positive Volunteers.

In individuals who are asymptomatic or in whom eggs can not be identified, serologic, i.e., antibody, testing may be a very useful tool in the diagnosis of schistosomiasis, yet its use is limited by the following:

- Serology may not become positive for *at least* 4-6 weeks after infection.
- Testing cannot distinguish *acute* from *chronic* infection. The presence of antibody is indicative only of schistosome infection at some time
- Antibodies may persist for years after parasitologic cure; thus, the test is *not* useful for individuals with a history of past disease and treatment.[10]

  Accordingly, serology cannot reliably differentiate ongoing or “active” infection, past infection but now cured by therapy, or reinfection after cure. Once an individual is antibody positive infection status is difficult to ascertain especially given the lower sensitivity of stool and urine examination.

Keeping these limitations in mind, positive schistosome serology in individuals with a history of freshwater exposure in an endemic area, no history of past schistosome

[10] “The duration of positive antibody test results after treatment is not known.” Marianne Wilson, Chief of Schistosomiasis Laboratory, Center’s for Disease Control and Prevention.

infections, and no prior treatment of disease, is considered presumptive evidence of infection and treatment should be initiated.

Serologic tests are often more sensitive than microscopic examination of stool and urine for eggs. Thus, if microscopic examination of stool and urine for eggs is negative or not available, *previously uninfected but potentially exposed or symptomatic individuals should always be tested for antibodies to schistosomes.*

Antibody Tests

The CDC performs an ELISA with purified adult worm antigens that is 99%, 90%, and 50% sensitive for *S. mansoni*, *S. haematobium* and *S. japonicum* respectively, and species-specific immunoblots for all three species that are at least 95% sensitive and 99% specific. A positive ELISA reaction (> 10 units/µl serum) indicates infection with *Schistosoma* species. Specificity of the ELISA for detecting schistosome infection is 99%.[11]

The Office of Medical Services recommends that PCMOs use the CDC for schistosomiasis antibody testing whenever possible. See Section 8.3 "CDC Antibody Testing Procedures" for specific procedures. Serologic tests performed in commercial laboratories or elsewhere in the world may not be as sensitive or specific or reliable.

Blood Tests and Chemistries

When schistosomiasis is suspected, the following laboratory tests should be performed as these tests may provide additional supportive evidence of infection:

- Complete Blood Count (CBC):
  - Peripheral eosinophilia is a common finding in most forms of schistosomiasis and may reach between 15-50%, particularly in acute infection. Eosinophilia, however, has a broad differential diagnosis and, in isolation, is not considered diagnostic of shistosomiasis, nor is it required for the diagnosis of schistosomiasis.

- Liver function tests (ALT, AST, GGT, alkaline phosphate, direct/indirect billirubin, albumin):
  - Alkaline phosphate and GGT may be increased with hepatic granulomatosis.
  - Transaminiases are generally not affected. Elevations may be caused by any coexisting hepatocellular disease, e.g., hepatitis.

Imaging Studies

Radiography is an important diagnostic tool in the evaluation of sequelae and complications of *chronic* schistosomiasis, however, radiographic findings are extremely

[11] The presence of antibody is indicative only of schistosome infection at some time and cannot be correlated with clinical status, worm burden, egg production, or prognosis.

rare in the usually, lightly infected, Volunteer population. Thus, the following exams should *not* routinely be performed.

- CXR, plain x-ray film of the abdomen, IVP, ultrasound, echocardiography, cystoscopy and endoscopy.
- CT scan and MRI; may, however, be useful in the evaluation of CNS disease.

As indicated, persistent or severe symptoms may require follow-up exams, e.g., cystoscopy, ultrasound or urologic evaluation for severe or persistent hematuria or other GU symptoms; endoscopy, ultrasound, or GI referral for severe or persistent blood in the stool or other GI symptoms.

5.4 Differential Diagnosis

Differential diagnosis of acute schistosomiasis includes other causes of fever of unknown origin including:

- Viral illness
- Allergic reaction
- Acute bacterial infection or bacterial sepsis
- Malaria

6. TREATMENT OF SCHISTOSOMIASIS

The Office of Medical Services bases its recommendations for the *treatment* of schistosomiasis on the most recent guidance from the CDC, a review of current literature, expert consensus opinion, and evidence-based guidelines where they exist.

There are two oral drugs currently available for the treatment of schistosomiasis – praziquantel and oxamniquine. Praziquantel is the current drug of choice for treating acute and chronic schistosomiasis based on its spectrum of activity, safety, and cost.

KEY PRINCIPALS OF SCHISTOSOMIASIS MANAGEMENT

- Recognize *early* infection due to schistosomiasis.
- Ensure adequate hydration and fever control.
- Consider corticosteroid support prior to treatment in heavily infected persons.
- Start treatment with Praziquantel, if indicated.
- Recognize, and provide therapy for, acute complications if present.
- Monitor the immediate and long-term clinical and parasitologic response to treatment.

Cercarial Dermatitis

- Treatment is symptomatic with oral antihistamines and topical hydrocortisone cream. Rarely, short courses of systemic steroids or antihistamines may be used to treat severely symptomatic individuals.
- Counseling regarding schistosomiasis prevention (see Section 4 above).

Acute Schistosomiasis

In general, *immediate* treatment is indicated and should be initiated when *one or more* of the following findings are present:

CRITERIA FOR IMMEDIATE TREATMENT

1. Eggs identified in the urine or stool.
2. Positive antibody serology in a *symptomatic* patient (see Section 5.3).
3. Positive history of exposure, AND signs and symptoms of acute disease (see Section 5.2), AND a strong clinical suspicion of schistosomiasis infection.

When microscopic examination of stool and urine for eggs is negative or not available, or when antibody titers are pending or indeterminate, PCMOs should *maintain a high index of suspicion of disease and consider treatment* when the following findings are present:

CRITERIA FOR TREATMENT CONSIDERATION
(High Index of Suspicion)

Positive history of exposure AND *one or more* of the following signs or symptoms of disease:

1. History of dermatitis and/or fever-like syndrome.
2. Hematuria - isolated hematuria, i.e., in the absence of other signs or symptoms of disease, is not considered diagnostic of schistosomiasis.
3. Eosinophillia - isolated eosinophilia, i.e., in the absence of other signs or symptoms of disease, is not considered diagnostic of schistosomiasis.
4. Any evidence of chronic schistosomal disease (see Section 5.1 above).

When initiating treatment, PCMOs must consider the following:

- *Acute schistosomiais is a serious disease and treatment should be initiated immediately,* regardless of time since exposure or schistosomal species.
- Adequate treatment, however, depends upon timing of treatment and schistosomal species. Therefore, if treatment was started earlier than 4-6 weeks after infection with

S. japonicum, 6-8 weeks after infection with *S. mansoni*, and 10-12 weeks after infection with *S. haematobium*, it should be *repeated within two to three months*. Treatment which occurs too early, i.e., during the prepatent phase of infection before adult worms have developed, which is also before egg production begins, may not be effective in curing schistosomiasis

- The Office of Medical Services also recommends treatment of any Volunteer whose antibody test results return ELISA (+) / immunoblot (-), and in whom there is a confirmed history of exposure.[12] Antibody testing should be repeated in 1 month to see if the immunoblot turns positive.
- Serology may take longer than the onset of acute symptoms to become positive.
- In the *acute stage eggs may not be present*, still, the presumptive diagnosis of acute schistosomiasis may be made on clinical suspicion reinforced by the presence of any of the above mentioned signs or symptoms of disease.
- When there is a high index of suspicion of disease and no laboratory confirmation of infection, PCMOs should consider repeat testing and OMS consultation.
- Section 6.2 and **ATTACHMENT D** provide additional guidance on the management of sero-positive Volunteers.

6.1 Immediate Management Measures

Once the diagnosis of acute schistosomiasis is made - presumptive or definitive - the following management measures should be employed:

- Ensure fever control.
- Ensure adequate hydration. Consider IV.
- Consider antibiotics and/or antimalarials as indicated.
- Monitor for acute complications, i.e., volume depletion and gastrointestinal (GI) bleeding, CNS.
- Be aware that treatment will not immediately relieve the symptoms of *acute* schistosomiasis as symptoms are due to an immunological reaction. Symptoms may transiently worsen as the killed worms release antigen increasing the strength of the immunological reaction.

6.2 In-Service Treatment of the Asymptomatic Antibody Positive Volunteer

Treatment, *at the time of diagnosis*, is recommended for all *asymptomatic* sero-positive Volunteers, even if parasitologic examinations are negative. This is important because

[12] This recommendation is based on the following CDC data: In the Volunteer population, approximately 5% of antibody test results return ELISA (+) / immunoblot (-); of those, one third seroconvert with repeat testing. The remaining 2% represents those with no infection or those possibly infected with *S. intercalatum* or *S. mekongi* – species for which the CDC test is not specific.

treatment decreases the chance of ectopic schistosomiasis, e.g., CNS disease, and stops or decreases egg formation.[13]

In-service treatment of asymptomatic antibody positive Volunteers should *not* be delayed until COS as it is impossible to predict with certainty if and when a Volunteer will develop symptoms and/or suffer the consequences of ectopic disease (see **ATTACHMENT D**). The likelihood of developing symptoms (see Section 5.1 above) is dependent not only on the unknowable size of the parasite burden at the time of infection but also on the unknowable variability in the individual's host immunity.

6.3 COS Management of Volunteers Treated In-Service for Schistosomiasis

All Volunteers treated in-service for schistosomiasis and remaining in endemic areas following treatment should be re-treated with praziquantel at COS (see **ATTACHMENT D**). In such Volunteers *repeat antibody testing at COS is not indicated and should not be performed.* These Volunteers are likely to remain antibody positive for many years and repeat testing will not assist in identifying new infection or response to therapy, i.e., titers will likely remain positive even if cure results (see Section 5.3 above).

Asymptomatic Volunteers with a history of in-service treatment should be instructed to take praziquantel at least 12[14] weeks after COS *or* their last potential exposure to contaminated water. Since praziquantel is effective only against adult worms, this pre-patent period of 12 weeks ensures that infecting cercariae have sufficient time to mature into adult worms prior to treatment." [15] No follow-up post treatment evaluations are indicated.

If a Volunteer with a history of in-service treatment for schistosomiasis is *symptomatic* for schistosomal disease at COS *and* they meet the criteria for treatment outlined above, they should be treated at the time of diagnosis, i.e., at COS. Treatment of a symptomatic Volunteer should never be delayed. This Volunteer should also be issued a PC-127C "Authorization for Payment of Medical/Dental Services" (127C) form for follow-up consultation and evaluation with a Primary Care physician or an Infectious Disease specialist.

[13] "The CDC and other experts recommend treatment for asymptomatic seropostive persons, even if parasitologic examinations are negative. The justification for this treatment approach is based on the following: (1) Antibody levels do not reliably decline even after successful therapy, thus there is no reliable method to differentiate successful cure versus reinfection in a seropositive person who has been reexposed to infected water; (2) Treatment prevents future morbidity due to schistosomiasis, e.g., genitourinary scarring, bladder cancer, CNS complications, hepatosplenomegalym and (3) Praziquantel is a safe drug for treating schistosomiasis. Serious adverse reactions are extremely rare." Adapted from document: *CDC Recommendations for Health Care Providers Evaluating Former Peace Corps Volunteers for Schistosomiasis.*

[14] Reviewers Cetron, Blackburn, and Addiss. 2005. "For the *asymptomatic* Volunteer, the length of time at which empiric COS treatment with prazaiquntel occurs, after continued exposure, should be at least as long as the longest species-specific pre-patent period, i.e., 10-12 weeks after exposure for *S. haematobium*.

6.4 Volunteer Education and Counseling

At the time of diagnosis, Medical Officers should strongly encourage the Volunteer to avoid repeated exposure to contaminated water and should review the disease prevention measures outlined in Section 4. In addition, Medical Officers should insure the Volunteer understands the following: (1) "the presence of anti-schistosomal antibodies does not reliably prevent re-infection"; (2) re-infection is possible and serious systemic complications, while infrequent, do occur; (3) further infection may not be detectable by currently available exams or tests; and (4) though empiric treatment may be attempted in the future, demonstration of re-exposure or cure may not be possible.

Volunteers who exhibit repeated high risk behavior through freshwater contact and do not comply with schistosomiasis prevention strategies due to willful misconduct or disregard for the Peace Corps Volunteer Health Program should be referred to the Country Director for administrative action (see TG 155 "Non-Compliance with Medical Policies or Instructions").

6.5 Treatment Regimens for Schistosomiasis

Any time treatment is initiated, PCMOs must document medication dose and frequency in the Volunteer health record.

- *Praziquantel* is the drug of choice for treating schistosomiasis. For uncomplicated schistosomiasis infections in Volunteers, OMS recommends the following treatment regimens:

S. haematobium, S. mansoni, and S. intercalatum

PRAZIQUANTEL 40 mg/kg/d in **two** (20 mg/kg doses) x 1 day 4-6 hours apart, with food

S. japonicum, S. mekongi

PRAZIQUANTEL 60 mg/kg/d in **three** (20 mg/kg doses) x 1 day 4-6 hours apart, with food

- *Oxamniquine* (Vansil) is an alternative drug for treating *S. mansoni* in areas where praziquantel is less effective.

OXAMNIQUINE 15 mg once (QD)[16]

[16] In East Africa, the dose should be increased to 30 mg/kg, and in Egypt and South Africa to 30 mg/kg/d x 2 d. Some experts recommend 40-60 mg/kg over 2-3 days in all of Africa (KC Shekhar, Drugs 1991; 42: 379). From "Drugs for Parasitic Infections", *The Medical Letter*, April 2002.

- *Steroids*

  Steroids have been used in the management of acute schistosomiasis, however, a significant number of patients have not been gathered to make a suitable clinical trial of any single treatment. Nevertheless, steroids may be useful prior to treatment in certain patients and PCMOs may want to consider their use.

  In general, steroids are used in heavily infected persons to control the immune response, as there may be a heightened immunologic reaction to worm antigens after praziquantel is given. Treatment may exacerbate symptoms as a result of increased antigen release or may produce a Loeffler-like syndrome in cases of heavy infestation, which may require pulmonary support.

  For persons with mild symptoms, non-steroidal anti-inflammatory agents should be used. Corticosteroids should be used only for persons who are extremely toxic appearing and whose symptoms fail to respond or worsen with treatment. A steroid course found useful by Gelfand et al. [17] is prednisone 5 mg tid for 3 days, 5 mg bid x 2 days, and 5 mg/day for 2 days.

6.6 Post-Treatment Follow-Up

The Office of Medical Services requires PCMOs to monitor Volunteers post treatment for symptom resolution and determination of cure. Medical Officers should do the following:

- *Reevaluate the Volunteer for resolution of symptoms*. Gross hematuria, dysuria, urinary frequency, and suprapubic pain usually respond rapidly to chemotherapy with praziquantal. Microscopic hematuria and/or protenuria may persist for several weeks following treatment, usually resolving within 6 months of treatment in > 90% of patients.[18]

  Persistent symptoms warrant follow-up exams as indicated, e.g., cystoscopy, ultrasound or urologic evaluation for hematuria or other GU symptoms; endoscopy or GI referral for blood in the stool or other GI symptoms, etc.

- If eggs were identified in urine or stool prior to treatment, *repeat urine or stool exams at 1-2 months and 3-4 months to confirm the disappearance of eggs* and to assess efficacy of treatment. Praziquantel is not 100% efficacious, therefore, if possible, PCMOs should monitor urine or stool for the disappearance of eggs.

- *Retreat if indicated.* Eggs may be shed for months after successful therapy or natural death of worms. Eggs may or may not be viable, but because the tests required to distinguish live from dead eggs, i.e., hatching assays, are not readily available, PCMOs should repeat treatment every few months until eggs are no longer detectable. Treatment should arrest egg laying, granuloma formation, and future complications.

[17] Gelfand. M., Glarke, de V., Bernberg, H. The Use of Steroids in the Earlier Hypersensitivity Stage of Schistosomiasis, *Central African Journal of Medicine*, Vol. 27, No. 11, 1981.
[18] Cetron, M. S., 1993.

- In those with *negative exams for eggs,* if praziquantel does not relieve the symptoms that are attributed to schistosomiasis, *consider another etiology*.
- *Do not repeat antibody testing*. Repeated antibody testing following treatment is not clinically indicated. Antibody levels are likely to persist for many years; the duration of positive antibody test following treatment is not known.

7. DRUGS USED IN THE TREATMENT OF SCHISTOSOMIASIS

7.1 Praziquantel

- *Effectiveness:* Praziquantel is active against all schistosomal species. It is also active against all clinical forms and stages of the disease except the developing worms, which are present during the first 4-6 weeks after infection with *S. japonicum*, 6-8 weeks after infection with *S. mansoni*, and 10-12 weeks after infection with *S. haematobium.*

  It *r*eliably cures 60-90% of patients and substantially decreases the worm burden and egg production in those who are not cured.[19] Cure rates are higher for those with light infections, such as Volunteers, than for those with high egg counts. Most patients with early disease and without severe end-organ complications recover completely. Hepatic granuloma from *S. mansoni* infection and *S. japonicum* infection and the urinary tract granuloma from *S. haematobium* infection may improve after successful treatment if reinfection is avoided.
- *Adverse Reactions:* Praziqantel is generally well tolerated. Reactions that are reported are usually mild and short-lived. Minor adverse reactions are observed in up to 50% of individuals; these include abdominal cramps or pain, dizziness, drowsiness, headache, sweating, dry mouth, dry eyes, and ringing or buzzing in the ears. Hives, itching, nausea, vomiting, diarrhea, anorexia and fever are occasionally reported.

  Peak serum levels occur 1-2 hours after each dose and the drug is rapidly metabolized and excreted. Transient liver enzyme elevations have been reported. Praziquantel is secreted in breast milk, it is metabolized by the liver, and its (inactive) metabolites are excreted in the urine. The drug's precise action on adult worms in unknown
- *Contraindications:* Documented hypersensitivity; ocular cysticercosis; in those persons coinfected with neurocysticercosis, seizures could be induced; hydantonins and systemic steroids may reduce serum praziquantel concentration possibly leading to treatment failures.

7.2 Oxamniquine (Vansil)

- Oxamniquine (Vansil): Alternative drug for treating infections caused by *S. mansoni* infection in areas in where praziquantel is less effective. It is very effective when given in appropriate doses (see Section 6.5 above). It is, generally, well tolerated with minor adverse reactions that include dizziness, drowsiness, and GI upset.

[19] Ross, A.G.P., Bartley, P. G., Sleigh, A. C. , et. al. Schistosomiasis, *New England Journal of Medicine,* Vol.. 346, No. 16, April 18, 2002, pg. 1218.

7.3 Other Drugs

- *Metrifonate* (see MSF Guide / Also recommended by WHO): Alternative drug for S. *haematobium* infection but is no longer available commercially. Requires multiple doses and is not active against *S. mansoni*. Not recommended by OMS.
- *Artemether*: currently being researched. Only drug effective against developing worms, as well as against adult worms. Not approved for use; concerns exist about induction of resistance, which would jeopardize the usefulness of this drug for malaria.

8. SCHISTOSOMIASIS ANTIBODY TESTING OF VOLUNTERS

8.1 In-Service Antibody Testing

In general, OMS *does not* recommend *mid-service* screening, via antibody testing, of Volunteers who are *asymptomatic* or "at-risk" of schistosomal disease. The Office of Medical Services does support risk-based screening, based on edemicity of disease and water exposure history, and *in-service* antibody testing when clinically indicated.

As such, in highly endemic areas where Volunteers are at significant risk of exposure and disease, PCMOs may conduct a mid-service risk assessment for freshwater exposure. If a history of exposure is reported during a mid-service exam or if a Volunteer *voluntarily* discloses a history of exposure during an in-service office visit, in-service antibody testing may be performed on a case-by-case basis. When an exposure history is reported or elicited, Volunteers should meet all of the criteria listed below before antibody testing is performed.

In addition, because serologic tests are often more sensitive than microscopic examination of stool and urine for eggs, if microscopic examination of stool and urine for eggs is negative or not available, *previously uninfected but potentially exposed, symptomatic individuals should always be tested for antibodies to schistosomes*.

CRITERIA FOR IN-SERVICE ANTIBODY TESTING OF VOLUNTEERS

1. No history of past schistosome disease, prior positive antibody test, or previous treatment for disease, AND
2. history (elicited or reported) of freshwater exposure in a schistosomiasis endemic area; OR disease specific symptoms (see Section 5.1 above) above, AND
3. if available, urine and stool microscopy have been performed and eggs cannot be demonstrated in specimens.

- Positive schistosome serology in individuals that meet the above criteria may be regarded as presumptive evidence of infection, and treatment should be initiated at the time of diagnosis.
- If test results return ELISA positive only and the Volunteer has a confirmed exposure history, treatment should be initiated. Antibody testing should be repeated in 1 month to see if the immunoblot turns positive.
- Blood samples for in-service schistosomiasis antibody testing should be drawn in country and sent to the CDC according to the procedures outlined below (see Section 8.3).

8.2 Close of Service Antibody Testing

The Office of Medical Services *requires* Volunteers who meet the following criteria be screened for schistosomal disease via antibody testing at COS, regardless of time in-service:

CRITERIA FOR COS ANTIBODY TESTING OF VOLUNTEERS

1. No history of past schistosome disease, prior positive antibody test, or previous treatment for disease, AND:
2. Volunteer service in Africa.[20]
3. Volunteer service in other schistosomiasis endemic areas.
4. Volunteer travel to schistosomiasis endemic areas during service AND documented history of freshwater exposure.

- *Antibody testing of Volunteers previously treated for schistosomiasis, e.g., during service, is not indicated and should not be performed.* These Volunteers are likely to remain antibody positive for many years and repeat testing does not assist in identifying new infection.
- All Volunteers previously treated for schistosomiasis, who may have been re-exposed to the disease prior to COS, should be re-treated with praziquantel at COS. Re-treatment is necessary as there are no currently available exams or tests to ascertain re-infection versus curative therapy (see also **ATTACHMENT D**).
- Asymptomatic, sero-positive Volunteers should be instructed to take praziquantel at least 12[21] weeks after COS or their last potential exposure to contaminated water. Since praziquantel is effective only against adult worms, this pre-patent period of 12

[20] Schistosomiasis testing is not required for Volunteers serving in Cape Verde unless there is a history of exposure or travel to an endemic area. If schistosomiasis testing is not performed, PCMOs must document the rational in the Volunteer's health record, e.g., "No history of exposure."
[21] Reviewers Cetron, Blackburn, and Addiss. 2005. "The length of time at which empiric COS treatment with prazaiquntel occurs, after continued exposure, should be at least as long as the longest species-specific pre-patent period, i.e., 10-12 weeks for *S. haematobium*.

weeks ensures that infecting cercariae have sufficient time to mature into adult worms prior to treatment." [22]

- Blood samples for COS schistosomiasis antibody testing should be drawn in country according to the procedures outlined below (see Section 8.3). If a sample cannot be obtained in country, PCMOs should issue a PC-127C form for consultation and evaluation with a Primary Care physician. The authorization should request the following:

  Office visits x 2 to obtain history of schistosomiasis exposure, symptoms and prior treatment; Obtain blood test for schistosomiasis and provide results and recommendations. No treatment authorized.

- The Post-Service Unit is responsible for review of schistosomiasis tests done at COS. The Post-Service Unit will contact those Volunteers whose test results indicate the need for further consultation and testing.

8.3 CDC Antibody Testing Procedures

All in-service and COS antibody testing must be conducted through the CDC using an enzyme-linked immunosorbent assay (ELISA) and immunoblot test (see Section 5.3 above for a test description).

When submitting specimens to the CDC, PCMOs should do the following:

- If drawing blood for in-service antibody testing, draw blood no sooner than 6 weeks post exposure for *S. mansoni, S. japonicum,* and *S. mekongi* and 10-12 weeks post exposure for *S. haematobium.*
- If drawing blood for COS schistosomiasis antibody testing, draw blood *within 1 week* of the Volunteer's scheduled departure.
- Submit blood in a serum separator tube. A tiger top tube is acceptable. Label the tube with a pre-printed label located in the Volunteer health record.
- To prevent bacterial growth in unrefrigerated specimens a preservative is recommended (see TG 360 "U.S. Laboratories").
- Include a CDC "Schistosomiasis Serology Submission Form" (**ATTACHMENT C**) with each blood sample(s).
- Insure specimens are clearly identified as in-service specimen or COS specimen by checking the appropriate box on the form.
- Attach the OMS supplied pre-printed label located in the Volunteer health record to the form. Verify the information on each label is accurate.

[22] Cetron, M., 1993. "Treatment at COS is optimal for asymptomatic seropositive Peace Corps Volunteers with 'non-patent' infection who currently cannot/do not avoid further "high-risk" water contact but are returning to the U.S. soon."

- Circle the location of exposure on the form, i.e., Africa, Asia, S. America, Middle East, Caribbean, so the appropriate schistosoma species will be tested for by immunoblot.
- File a copy of the completed submission form **(ATTACHMENT C)** in the Volunteer health record.
- Send blood samples for schistosomiasis antibody testing to the CDC at the following address (see also table in TG 360.3 "U.S. Labs and Services").

DASH - Parasitology
CDC MS G-12
1600 Clifton Road
Atlanta, GA 30333 USA
Attention: Lab Specimen

- Medical officers should not use 127C or 209B "Authorization for Volunteer Medical Examination and Labs" (209B) forms to authorize routine schistosomiasis testing at COS unless it is impossible to obtain a sample in country.

9. TREATMENT OF PREGNANT VOLUNTEERS

Medical Officers are required to consult OMS if a pregnant Volunteer develops schistosomiasis. Praziquantel is the OMS preferred drug of choice. Physicians may prefer to defer treatment until after the first trimester.

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